Remarks

Claims 20-24, 32 and 43-57 are pending in the present application. Applicants have made an amendment to the specification to correct obvious typographical errors. No new matter is added.

Claims 43-57 are rejected under 35 U.S.C. §112, first paragraph as not enabled by the specification. The Office has reasoned that the specification enables methods for deleting a marker sequence from a DNA sequence that has been introduced into a mouse genome using a gamete-specific promoter by growing the mouse cell so that the recombinase is expressed during gametogenesis, and deleting the marker gene in the resulting gametes, and mice comprising the DNA described above. The Office objects to the perceived breadth of the claims with respect to a regulatable promoter.

The Office asserts that the specification contemplates that a wild-type allele may be used in gene therapy, which is not enabled, and that the broad claims encompass tissue-specific promoters but are not limited to them. The Office also comments that the specification provides guidance with respect to deleting a gene upon the expression of Cre, which would not be possible with any promoter, as claimed. The Office further states that a tissue-specific promoter is required and that the specification provides guidance only for gamete-specific promoters.

Applicants have amended the independent claims herein to recite a "spatially or temporally restricted promoter," operably linked to a recombinase gene. The claims thus now are limited to promoters that are spatially (tissue)-restricted or temporally

restricted. Support for this language may be found in the specification as filed, at page 8, lines 3-6, which refers to the restricted spatial or temporal expression of the recombinase. As well, the art had described many such promoters and the specification also provides ample description of various restricted promoters, for example at page 2, second paragraph, which describes the use of gamete and somatic tissue-specific promoters to drive expression of the recombinase. Applicants respectfully urge that the promoters of the amended claims are fully supported by the specification as filed and that the skilled person would be able to use any known spatially or temporally restricted promoter, without undue experimentation, to make and use the claimed nucleic acid molecules to excise sequences that have been inserted into a cell.

The Office has commented that the promoter must be active only after birth, or a transgenic animal would not arise. Office Action, page 5. This statement indicates that the Office considers generation of an animal born with the promoter inactive to be necessary for operation of the method. The method of amended claim 43, here rejected, involves deleting a nucleic acid sequence using a recombinase expressed in a spatially or temporally restricted manner so that the nucleic acid in question is removed from the genome in a specific tissue or at a specific time. If the promoter is active before birth of an animal, the method is still achieved, since the nucleic acid sequence is deleted in a manner regulated by the promoter (for example in a specific tissue but not in all tissues) whether the animal which contains the mouse cell genome is born at the time or not. If the promoter is tissue-specific, the animal referred to by the Office would be a transgenic animal that lacks the nucleic acid

in question in that particular tissue, for example muscle tissue (specification, page 2, line 13). If the promoter is temporally-restricted, the nucleic acid is removed at a particular time--prior to that time the cell or embryo or animal would have been transgenic. Since the claims are not restricted and does not even necessarily relate to animals that are born alive, Applicants submit that this concept is not relevant in evaluating the present claims.

Applicants also believe that the amendments to the claims discussed above eliminate the concerns expressed by the Office with respect to the types of genes and nucleic acids which are deleted by the method. The material to be deleted is that which is flanked by recombinase sites, as the specification makes clear. Therefore when the recombinase is activated by the promoter under the proper circumstances for that promoter's action, the nucleic acid sequence between the recombinase sites will be excised, whether it is a marker gene or any gene. Any nucleic acid sequence can be placed between recombinase sites and therefore can be removed by the method. Applicants submit that any nucleic and sequence thus is enabled.

The ability to detect the operation of the recombinase is not part of the method. Nevertheless, it would be a matter of mere routine for the skilled artisan to confirm deletion of the nucleic and sequence either by using a marker gene, specific probes that are complimentary to the sequence which is excised, or non-specific methods such as detecting fragment length or molecular weight changes (see Figure 2 and accompanying text at page 3). No experimentation would have been necessary to perform

these methods and the skilled practitioner would be assured that the excision had been made.

For the above reasons, Applicants request that the rejection on grounds of lack of enablement be withdrawn at this time.

Claims 20-24 and 32 are rejected under 35 U.S.C. §112, second paragraph as indefinite. The Office essentially has objected to the use of the phrases "nucleic acid molecule" and "nucleic acid sequence" in claim 20 to refer to two different things, which causes confusion as to what nucleic acid is to be removed. Applicants have amended the claims to avoid use of both these phrases together and therefore request that the Examiner withdraw this rejection. The phrase "nucleic acid molecule" is replaced by "DNA molecule." In addition, the amendments clarify the distinctness between the nucleic acid sequence to be removed and the DNA molecule that comprises this nucleic acid sequence. The claims clearly refer to removal of the nucleic acid sequence, while the "DNA molecule" comprises said nucleic acid sequence to be removed and other recited components. This language more closely tracks that used in claim 43, in which a nucleic acid sequence (which is part of a DNA molecule) is deleted. Applicants believe the skilled person reading these claims would clearly understand the method and what is to be removed. Support for these amendments may be found throughout the specification, which repeatedly refers to specific removal of nucleic acid sequences, and inter alia at page 2, lines 2-4 and page 5, line 9.

The claim also has been amended to more clearly indicate that the recombinase sites flank both the (1) recombinase gene

and its linked promoter and (2) the DNA to be removed and deletes the requirement that the components flanked by the recombinase sites are in a defined order. Support for this amendment can be found throughout the specification and inter alia at page 5, lines 18 and 26, page 7, line 25 and page 8, line 21, which discuss flanking loxP or recombogenic sites. The phrase "sequential order" is not found in the specification. Moreover, it is clear to one of skill in the art that action of the recombinase will excise material flanked by the recombinase sites regardless of the sequential order of the recombinase gene and any other DNA also flanked by the recombinase sites. Applicants submit that the claims fully comply with the requirement for definiteness.

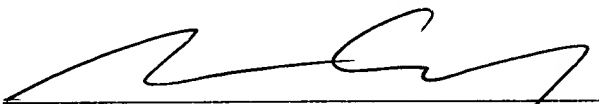
Applicants request that the Office now withdraw the rejection of these claims on grounds of indefiniteness.

Claims 20-24, 32 and 43-45 are rejected under 35 U.S.C. §102(b) as anticipated by Russ et al. for the reasons of record, which do not include any citation for disclosure of a spatially or temporally restricted promoter. For a reference to anticipate a claim, it must contain, within its four corners, each and every element of the rejected claim. M.P.E.P. §2131. Failing that, the rejection is improper.

Applicants respectfully submit that the amendments to the claims discussed above obviate the rejection over the Russ et al. reference. Russ et al. do not discuss the spatially or temporally restricted promoter recited by the amended claims and therefore lack at least one required claim element--the genetic elements introduced by Russ et al. result in transient expression

with no spatial or temporal restriction. To use a promoter with activity restricted in time or by tissue would not achieve the goal of the Russ et al. method, which is to remove all viral sequences throughout the treated organism. Therefore, the methods and constructs disclosed by Russ et al. cannot include a spatially or temporally restricted promoter and therefore cannot anticipate the claims of the present application. For these reasons, Applicants request that the Office withdraw the rejection of claims as anticipated by Russ et al.

Respectfully submitted,

By 

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